(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 341 551 A1**

F8

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: 89107912.1

(22) Date of filing: 02.05.89

(51) Int. Cl.4: C07C 63/66 , C07C 65/28 , C07C 69/94 , C07F 9/28 , C07C 51/00 , C07C 67/00 , C07C 149/273 , A61K 31/19 , A61K 31/235

(30) Priority: 13.05.88 GB 8811423

(43) Date of publication of application: 15.11.89 Bulletin 89/46

(84) Designated Contracting States: AT BE CH DE ES FR GB GR IT LI NL SE

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(54) **Alkenoic acid derivatives.**

(57) New alkenoic acid derivatives can be prepared by reaction of corresponding aldehydic esters with phosphorous compounds in inert solvents and in the presence of bases followed by hydrolysis of the intermediate esters. The new alkenoic acid derivatives can be used as active compounds in medicaments.

EP 0 341 551 A1

LeA 25722 = US patents 5041638
5159097
5221760

United States Patent [19]

Rosentreter et al.

[11] **Patent Number: 5,041,638**

[45] **Date of Patent: Aug. 20, 1991**

[54] ALKENOIC ACID DERIVATIVES

[75] Inventors: **Ulrich Rosentreter**, Wuppertal, Fed. Rep. of Germany; **Harold C. Kluender**, West Haven, Conn.; **Trevor S. Abram**, Marlow Bucks, United Kingdom; **Peter Norman**, Cippenham, United Kingdom; **Steven R. Tudhope**, Windsor, United Kingdom

[73] Assignee: **Bayer Aktiengesellschaft**, Leverkusen, Fed. Rep. of Germany

[21] Appl. No.: **349,371**

[22] Filed: **May 9, 1989**

[30] **Foreign Application Priority Data**

May 13, 1988 [GB] United Kingdom 8811423

[51] **Int. Cl.**[5] **C07C 59/00**

[52] **U.S. Cl.** **562/465**; 560/11; 560/12; 560/15; 560/17; 560/21; 560/22; 560/23; 560/60; 560/61; 560/62; 560/64; 560/54; 562/426; 562/429; 562/430; 562/433; 562/434; 562/435; 562/438; 562/443; 562/444; 562/449; 562/457; 562/470; 562/471; 562/472

[58] **Field of Search** 562/465, 426, 429, 430, 562/433, 434, 435, 438, 443, 444, 449, 457, 470, 471, 472; 560/11, 12, 15, 17, 21, 22, 23, 54, 60, 61, 62, 64; 514/532, 534, 539, 535, 561, 562, 564, 568, 567

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

0084667 8/1983 European Pat. Off. .

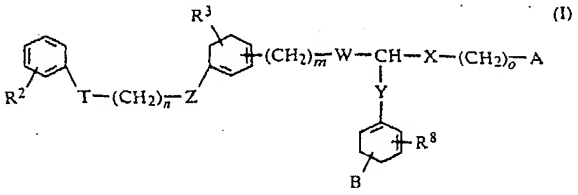
2184121 6/1987 United Kingdom .

Primary Examiner—Paul J. Killos

Attorney, Agent, or Firm—Sprung Horn Kramer & Woods

[57] ABSTRACT

An alkenoic acid derivative of the formula



(I)

in which

X and Y are identical or different and represent sulfur, sulfoxide, sulfone, an alkylene chain, —SCH_2—, or oxygen or a direct bond,

W represents —CH=CH— or —CH_2—CH_2—,

o represents a number 1 to 5,

A and B are identical or different and represent carboxyl, carboxymethylene, tetrazolyl or tetrazolylmethylene, or —CO_2R^9 or —$CH_2CO_2R^9$ or —$CONR^{10}R^{11}$ or nitrile

n represents a number 1 to 10,

m represents a number 0 to 7,

T and Z are identical or different and represent oxygen or a direct bond and

R^2, R^3, R^8 are identical or different and represent hydrogen, alkyl, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano or nitro and

R^9 is lower alkyl and R^{10} and R^{11} are hydrogen, lower alkyl, alkylsulfonyl or arylsulfonyl or together are an alkylene chain to form a ring

and pharmaceutically acceptable salts thereof. Such alkenoic acid derivatives are useful as leucotriene disease antagonists.

11 Claims, No Drawings

EXAMPLE 145

Animals-Male Dunkin Hartley 350–400 g (Interfauna).

1. Preparation

A guinea-pig was killed by a blow to the head and the trachea placed in Tyrodes solution plus indomethacin (3×10^{-6}M). The trachea was cut open longitudinally opposite the trachealis muscle and alternating transverse cuts made across three quarters of the tissue width. The preparation was opened out as a zig-zag-chain and suspended in a 10 ml tissue-bath containing Tyrodes solution with indomethacin (3×10^{-6}M) at 37° C. gassed with 5% CO_2 in oxygen. Tissue movement was monitored with a Hugo Sachs isotonic transducer with a load of 250–500 mg.

2. Experimental Procedure

Upon equilibration maximal response was determined using 10^{-4} and 3×10^{-4}M histamine. The histamine was washed out and Tyrodes exchanged for Tyrodes plus indomethacin, L-serine borate (45 mM) and L-cysteine (10 mM). When the tissues had re-equilibrated one of each set of four preparations was treated with a series of 10 μl volumes of the vehicle control EtOH. The other three were each treated with cumulative additions of the test drug to give a tissue-bath concentration from 10^{-11}–10^{-5}M. Fifteen minutes after the final addition of test drug or EtOH a cumulative concentration response curve for LTD_4 (10^{-10}–10^{-6}M) was applied. When maximal LTD_4-concentration was reached the tissues were discarded.

3. Materials

Indomethacin, LTD_4 (Leukotrien D_4), boric acid, L-cysteine and L-serine.

Tyrodes solution consisted of the following ANALAR grade substances (mM) dissolved in distilled water: NaCl 137, $MgCl_2$ 2.1, KCl 2.7, NaH_2DO_4 0.5, $CaCl_2$ 2.4, $NaHCO_3$ 11.9, D-glucose 9.2.

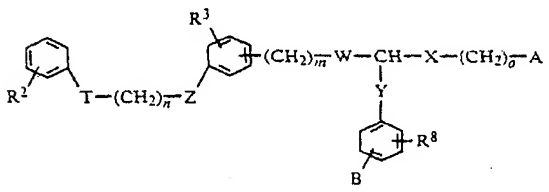
RESULTS

Contractions were normalised to the histamine-induced maximum for each preparation. The responses to analogue, LTD_4 and LTD_4 plus analogue were then expressed as a percentage of the maximum LTD_4 response in the appropriate control preparation. EC_{50} (that concentration required to induce a 50% maximal LTD_4 response) values for 'test' and control tissues were calculated using a least squares linear regression program. These values were used to calculate a pK_B to quantify the degree of antagonism where appropriate.

It will be appreciated that the instant specification and claims are set forth by way of illustration and not limitation, and that various modifications and changes may be made without departing from the spirit and scope of the present invention.

What is claimed is:

1. An alkenoic acid derivative of the formula



(I)

in which

X and Y are identical or different and represent sulfur, sulfoxide, sulfone, an alkylene chain, —SCH_2—, or oxygen or a direct bond,

W represents —CH=CH— or —CH_2—CH_2—,

o represents a number 1 to 5,

A and B are identical or different and represent carboxyl, carboxymethylene, or —CO_2R^9 or —$CH_2CO_2R^9$

n represents a number 1 to 10,

m represents a number 0 to 7,

T and Z are identical or different and represent oxygen or a direct bond and

R^2, R^3, R^8 are identical or different and represent hydrogen, alkyl, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano or nitro and

R^9 is lower alkyl and,

and salts thereof.

2. An alkenoic acid derivative according to claim 1, wherein

X and Y are identical or different and represent sulfur, sulfoxide, sulfone, a methylene group, —SCH_2—, oxygen, an ethylene group or a direct bond,

W represents —CH=CH— or —CH_2CH_2—,

o represents a number 1 to 4,

n represents a number 1 to 7,

m represents a number 0 to 5,

T and Z are identical or different represent oxygen or a direct bond and

R^2, R^3, R^8 are identical or different and represent hydrogen, lower alkyl, lower alkoxy, fluorine, chlorine or trifluoromethyl.

3. An alkenoic acid derivatives according to claim 1, wherein

X represents sulfur, sulfone or a methylene group,

Y represents sulfur, a methylene group, —SCH_2— or a direct bond,

W represents —CH=CH—,

R^8 and R^3 represents H,

R^2 represents H or F,

o represents a number 1, 2, 3 or 4,

n represents a number 2, 3, 4, 5, 5 or 6,

m represents a number 0, 1 or 2,

T represents oxygen or a direct bond,

Z represents oxygen or a direct bond and

A represents carboxyl or ester thereof,

B represents para carboxyl or ester thereof.

4. A leucotriene disease antagonist composition comprising a leucotriene disease antagonistic effective amount of an alkenoic acid derivative according to claim 1 in admixture with a pharmaceutically acceptable carrier.

5. A composition according to claim 4 comprising 0.5 to 98 weight % of the alkenoic acid.

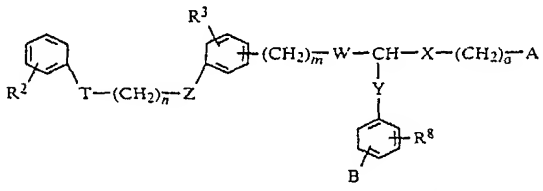
6. A unit dose of a composition according to claim 4 in the form of a tablet or a capsule.

7. A method of treating a patient suffering from a leucotriene disease comprising administering to said patient a leucotriene disease antagonistic effective amount of an alkenoic acid derivative according to claim 1.

8. A method according to claim 7 wherein the leucotriene disease is a circulatory disease.

9. A method according to claim 7, wherein the leucotriene disease is a respiratory disease.

10. A process for the preparation of an alkenoic acid derivative of the formula



(I)

in which

X and Y are identical or different and represent sulfur, sulfoxide, sulfone, an alkylene chain, —SCH$_2$—, oxygen or a direct bond,

W represents —CH=CH— or —CH$_2$—CH$_2$—,

o represents a number 1 to 5,

A and B are identical or different and represent carboxyl, carboxymethylene, or —CO$_2$R^9 or —CH$_2$CO$_2$R^9 or

n represents a number 1 to 10,

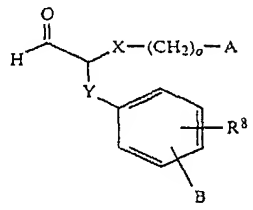
m represents a number 0 to 7,

T and Z are identical or different and represent oxygen or a direct bond and

R^2, R^3, R^8 are identical or different and represent hydrogen, alkyl, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano or nitro

and their salts, comprising reacting

an aldehyde of the formula (II)



(II)

in which

X, Y, o and R^8 have the above mentioned meanings and

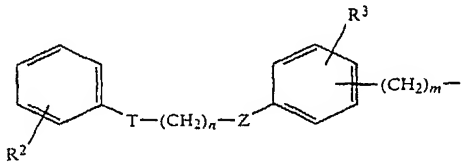
A and B are identical or different and represent CO$_2$R^9 or CH$_2$CO$_2$R^9 or wherein R^9 represents lower alkyl and,

with a phosphorus compound of the formula (III)

$$R^1—CH_2—U \qquad (III)$$

in which

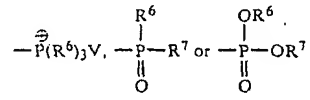
R^1 is



in which

R^2, T, n, Z, R^3 and m have the above mentioned meanings and

U represents a group of the formula



where

R^6 and R^7 are identical or different and denote alkyl or phenyl and

V denotes a halide anion or a tosylate anion, in an inert solvent in the presence of a base,

whereby the esters are then hydrolyzed or partially hydrolyzed.

11. A process according to claim **10**, wherein the process is carried out in the temperature range from −80° C. to +70° C.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

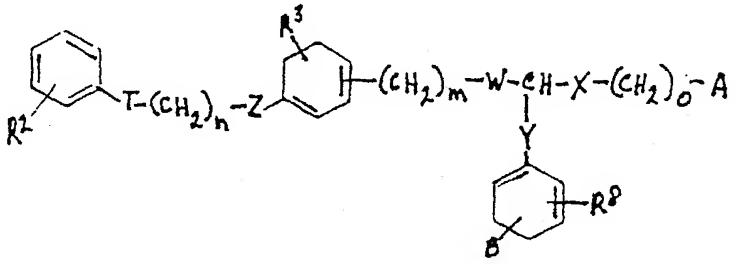
PATENT NO. : 5,041,638

DATED : August 20, 1991

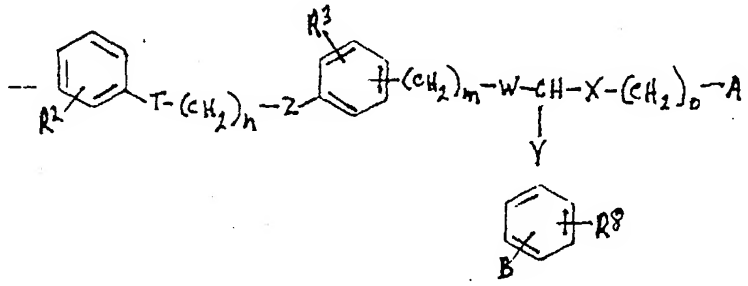
INVENTOR(S) : Rosentreter et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page — item [57] ABSTRACT: Line 2 delete

"  (I) "

and substitute

--  (I) --

Col. 78, line 17 — After " alkyl " delete " and " and substitute -- , --

Col. 79, line 20 — Delete " or " and insert -- wherein R^9 is lower alkyl and --

Col. 80, line 4 — Delete second " or "

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,041,638

DATED : August 20, 1991

INVENTOR(S) : Rosentreter et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 80, line 5 Delete " and "

Signed and Sealed this

Twenty-eighth Day of September, 1993

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

US005159097A

United States Patent [19]

Rosentreter et al.

[11] Patent Number: 5,159,097

[45] Date of Patent: Oct. 27, 1992

[54] ALKENOIC ACID DERIVATIVES

[75] Inventors: **Ulrich Rosentreter**, Wuppertal, Fed. Rep. of Germany; **Harold C. Kluender**, West Haven, Conn.; **Trevor S. Abram**, Marlow Bucks, United Kingdom; **Peter Norman**, Slough, United Kingdom; **Steven R. Tudhope**, Windsor, United Kingdom

[73] Assignee: **Bayer Aktiengesellschaft**, Leverkusen, Fed. Rep. of Germany

[21] Appl. No.: **618,184**

[22] Filed: **Nov. 26, 1990**

Related U.S. Application Data

[62] Division of Ser. No. 349,371, May 9, 1989, Pat. No. 5,041,638.

[30] **Foreign Application Priority Data**

May 13, 1988 [GB] United Kingdom 8811423

[51] **Int. Cl.**[5] **C07F 9/02**

[52] **U.S. Cl.** **558/167**; 558/197; 562/8; 562/12; 562/20; 562/23

[58] **Field of Search** 558/167, 197; 562/8, 562/12, 20, 23

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

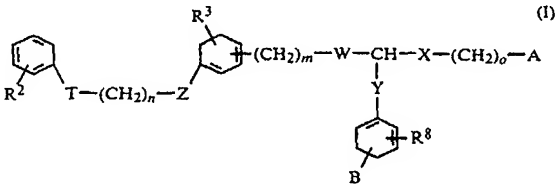
8605779 10/1980 World Int. Prop. O. .

Primary Examiner—Paul J. Killos

Attorney, Agent, or Firm—Sprung, Horn, Kramer & Woods

[57] **ABSTRACT**

An alkenoic acid derivative of the formula



(I)

in which

X and Y are identical or different and represent sulfur, sulfoxide, sulfone, an alkylene chain, $-SCH_2-$, or oxygen or a direct bond,

W represents $-CH=CH-$ or $-CH_2-CH_2-$,

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A and B are identical or different and represent carboxyl, carboxymethylene, tetrazolyl or tetrazolylmethylene, or $-CO_2R^9$ or $-CH_2CO_2R^9$ or $-CONR^{10}R^{11}$ or nitrile

n represents a number 1 to 10,

m represents a number 0 to 7,

T and Z are identical or different and represent oxygen or a direct bond and

R^2, R^3, R^8 are identical or different and represent hydrogen, alkyl, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano or nitro and

R^9 is lower alkyl and R^{10} and R^{11} are hydrogen, lower alkyl, alkylsulfonyl or arylsulfonyl or together are an alkylene chain to form a ring

and pharmaceutically acceptable salts thereof. Such alkenoic acid derivatives are useful as leucotriene disease antagonists.

1 Claim, No Drawings

width. The preparation was opened out as a zig-zag-chain and suspended in a 10 ml tissue-bath containing Tyrodes solution with indomethacin (3×10^{-6}M) at 37° C. gassed with 5% CO_2 in oxygen. Tissue movement was monitored with a Hugo Sachs isotonic transducer with a load of 250–500 mg.

2. Experimental Procedure

Upon equilibration maximal response was determined using 10^{-4} and 3×10^{-4}M histamine. The histamine was washed out and Tyrodes exchanged for Tyrodes plus indomethacin, L-serine borate (45 mM) and L-cysteine (10 mM). When the tissues had re-equilibrated one of each set of four preparations was treated with a series of 10 μl volumes of the vehicle control EtOH. The other three were each treated with cumulative additions of the test drug to give a tissue-bath concentration from 10^{-11}–10^{-5}M. Fifteen minutes after the final addition of test drug or EtOH a cumulative concentration response curve for LTD_4 (10^{-10}–10^{-6}M) was applied. When maximal LTD_4-concentration was reached the tissues were discarded.

3. Materials

Indomethacin, LTD_4 (Leukotrien D_4), boric acid, L-cysteine and L-serine.

Tyrodes solution consisted of the following ANALAR grade substances (mM) dissolved in distilled water: NaCl 137, $MgCl_2$ 2.1, KCl 2.7, NaH_2DO_4 0.5, $CaCl_2$ 2.4, $NaHCO_3$ 11.9, D-glucose 9.2.

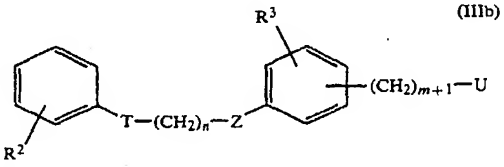
RESULTS

Contractions were normalised to the histamine-induced maximum for each preparation. The responses to analogue, LTD_4 and LTD_4 plus analogue were then expressed as a percentage of the maximum LTD_4 response in the appropriate control preparation. EC_{50} (that concentration required to induce a 50% maximal LTD_4 response) values for 'test' and control tissues were calculated using a least squares linear regression program. These values were used to calculate a pK_B to quantify the degree of antagonism where appropriate.

It will be appreciated that the instant specification and claims are set forth by way of illustration and not limitation, and that various modifications and changes may be made without departing from the spirit and scope of the present invention.

What is claimed is:

1. A phosphorous compound of the formula

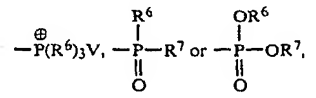


(IIIb)

wherein

R^2 and R^3 are identical or different and represent hydrogen, alkyl, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano or nitro,

U represents a group of the formula



where

R^6 and R^7 are identical or different and denote alkyl or phenyl and

V denotes tosylate anion,

T and Z are identical or different and represent oxygen or a direct bond,

m represents a number 0 to 7 and

n represents a number 1 to 10.

* * * * *

US005221760A

United States Patent [19]

Rosentreter et al.

[11] Patent Number: 5,221,760

[45] Date of Patent: Jun. 22, 1993

[54] ALKENOIC ACID DERIVATIVES

[75] Inventors: **Ulrich Rosentreter**, Wuppertal, Fed. Rep. of Germany; **Harold C. Kluender**, West Haven, Conn.; **Trevor S. Abram**, Marlow Bucks, United Kingdom; **Peter Norman**, Slough, United Kingdom; **Steven R. Tudhope**, Windsor, United Kingdom

[73] Assignee: **Bayer Aktiengesellschaft**, Leverkusen, Fed. Rep. of Germany

[21] Appl. No.: **891,629**

[22] Filed: **Jun. 1, 1992**

Related U.S. Application Data

[62] Division of Ser. No. 618,184, Nov. 26, 1990, Pat. No. 5,159,097, which is a division of Ser. No. 349,371, May 9, 1989, Pat. No. 5,041,638.

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May 13, 1988 [GB] United Kingdom 8811423

[51] **Int. Cl.**[5] **C07C 303/00**

[52] **U.S. Cl.** **558/58**

[58] **Field of Search** 558/58

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

0084667 8/1983 European Pat. Off. .
2184121 6/1987 United Kingdom .

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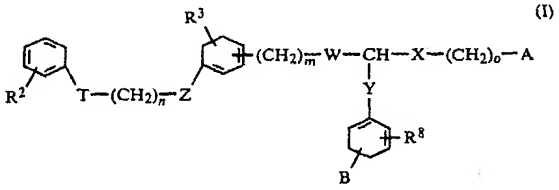
E. J. Corey et al, Chem. Ber. 111, 1337, 1363 (1978).
D. Enders et al, Org. Synth. 65, 183 (1987).

Primary Examiner—Paul J. Killos
Attorney, Agent, or Firm—Sprung Horn Kramer & Woods

[57] **ABSTRACT**

An alkenoic acid derivative of the formula



(I)

in which
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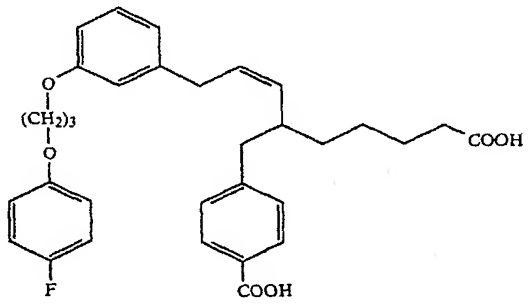
W represents —CH=CH— or —CH_2—CH_2—,
o represents a number 1 to 5,
A and B are identical or different and represent carboxyl, carboxymethylene, tetrazolyl or tetrazolylmethylene, or —CO_2R^9 or —$CH_2CO_2R^9$ or —$CONR^{10}R^{11}$ or nitrile
n represents a number 1 to 10,
m represents a number 0 to 7,
T and Z are identical or different and represent oxygen or a direct bond and
R^2, R^3, R^8 are identical or different and represent hydrogen, alkyl, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano or nitro and
R^9 is lower alkyl and R^{10} and R^{11} are hydrogen, lower alkyl, alkylsulfonyl or arylsulfonyl or together are an alkylene chain to form a ring

and pharmaceutically-acceptable salts thereof. Such alkenoic acid derivatives are useful as leucotriene disease antagonists.

8 Claims, No Drawings

EXAMPLE 144

6-(4-Carboxybenzyl)-9-{3-[3-(4-fluorophenoxy)-propoxy]benzyl}-7-(Z)-nonenoic acid



Using the ester product of Example 143 and the procedure of example 68 the title compound was prepared.

Yield: 85% of theory.

NMR ($CDCl_3$, 300 MHz): 1.2–1.7[6] m, 2.23[2] q, J=8 Hz, 2.33[2] t, J=8 Hz, 2.5–2.8[3] m, 3.03[1] dd, J=14.8 Hz, 3.14[1] dd, J=14.8 Hz, 4.04–4.15[4] m, 5.22[1] t, J=10 Hz, 5.54[1] dt, J=10.7 Hz, 6.5–7.3[10] m, 7.97[2] d, J=8 Hz.

EXAMPLE 145

Animals-Male Dunkin Hartley 350–400 g (Interfauna).

1. Preparation

A guinea-pig was killed by a blow to the head and the trachea placed in Tyrodes solution plus indomethacin (3×10^{-6}M). The trachea was cut open longitudinally opposite the trachealis muscle and alternating transverse cuts made across three quarters of the tissue width. The preparation was opened out as a zig-zag-chain and suspended in a 10 ml tissue-bath containing Tyrodes solution with indomethacin (3×10^{-6}M) at 37° C. gassed with 5% CO_2 in oxygen. Tissue movement was monitored with a Hugo Sachs isotonic transducer with a load of 250–500 mg.

2. Experimental Procedure

Upon equilibration maximal response was determined using 10^{-4} and 3×10^{-4}M histamine. The histamine was washed out and Tyrodes exchanged for Tyrodes plus indomethacin, L-serine borate (45 mM) and L-cysteine (10 mM). When the tissues had re-equilibrated one of each set of four preparations was treated with a series of 10 µl volumes of the vehicle control EtOH. The other three were each treated with cumulative additions of the test drug to give a tissue-bath concentration from 10^{-11}–10^{-5}M. Fifteen minutes after the final addition of test drug of EtOH a cumulative concentration response curve for LTD_4 (10^{-10}–10^{-6}M) was applied. When maximal LTD_4-concentration was reached the tissues were discarded.

3. Materials

Indomethacin, LTD_4 (Leukotrien D_4), boric acid, L-cysteine and L-serine.

Tyrodes solution consisted of the following ANALAR grade substances (mM) dissolved in distilled water:NaCl 137, $MgCl_2$ 2.1, KCl 2.7, NaH_2DO_4 0.5, $CaCl_2$ 2.4, $NaHCO_3$ 11.9, D-glucose 9.2.

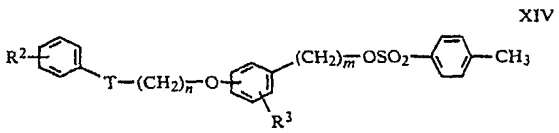
RESULTS

Contractions were normalised to the histamine-induced maximum for each preparation. The responses to analogue, LTD_4 and LTD_4 plus analogue were then expressed as a percentage of the maximum LTD_4 response in the appropriate control preparation. EC_{50} (that concentration required to induce a 50% maximal LTD_4 response) values for 'test' and control tissues were calculated using a least squares linear regression program. These values were used to calculate a pK_B to quantify the degree of antagonism where appropriate.

It will be appreciated that the instant specification and claims are set forth by way of illustration and not limitation, and that various modifications and changes may be made without departing from the spirit and scope of the present invention.

What is claimed is:

1. A compound having the formula:



XIV

in which

R^2 represents hydrogen, alkyl, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano or nitro;

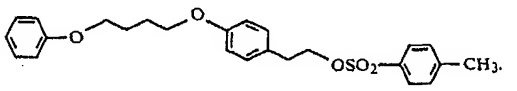
T represent oxygen or a direct bond;

n represents a number 1 to 10;

R^3 represents hydrogen, alkyl, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano or nitro; and

m represents a number 0 to 7.

2. The compound according to claim 1, having the formula:



3. A leucotriene disease antagonist composition comprising a leucotriene disease antagonistic effective amount of an alkenoic acid derivative according to claim 1 in admixture with a pharmaceutically acceptable carrier.

4. A composition according to claim 3 comprising 0.5 to 98 weight % of the alkenoic acid.

5. A unit dose of a composition according to claim 3 in the form of a tablet or a capsule.

6. A method of treating a patient suffering from a leucotriene disease comprising administering to said patient a leucotriene disease antagonistic effective amount of an alkenoic acid derivative according to claim 1.

7. A method according to claim 6 wherein the leucotriene disease is a circulatory disease.

8. A method according to claim 6, wherein the leucotriene disease is a respiratory disease.

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